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10/659,705	09/11/2003	A. Thomas Look	112706.123US2	6046

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WILMER CUTLER PICKERING HALE AND DORR LLP
1875 PENNSYLVANIA AVE., NW
WASHINGTON, DC 20004

EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
06/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
tina.dougal@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	10/659,705	LOOK ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/22/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,31-59 and 67-74* is/are pending in the application.

4a) Of the above claim(s) *3,38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,31-37,39-59 and 67-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/24/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 03/22/2007 has been received. Claims 25-30 and 60-66 have been cancelled. Claims 3 and 38 are withdrawn as being drawn to nonelected species. Claims 1,24,35,36 and 74 are amended. Claims 1-24,31-59 and 67-74 are pending. Claims 1,2,4-24,31-37 and 39-74 are under consideration in the instant office action.

Specification

The objection to the specification is withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1,2,4-24,31-37, 39-59 and 67-74 remain rejected under 35 U.S.C. 112, first paragraph. The specification, while being enabling for 1) a transgenic fish whose genome comprises a transgene comprising a cMyc gene operably linked to the Rag2 promoter wherein cMyc is expressed in T-lymphocytes of the fish resulting in cMyc-induced T-cell lymphoblastic leukemia and 2) a method of screening drugs or agents that mediate cMyc-induced T-cell lymphoblastic leukemia comprising contacting said transgenic fish with a test drug or agent and comparing the phenotype of said contacted fish to that of said fish prior to contact with said test drug or agent , wherein a decrease in cMyc-induced lymphoblastic leukemia in the contacted fish compared to that prior to contact with said test drug or agent indicates a potential drug or agent for decreasing cMyc-mediated T-cell lymphoblastic leukemia, does not reasonably provide enablement for 1) a transgenic fish whose genome comprises any oncogene operably

linked to any promoter wherein the oncogene is not expressed and does not cause T-cell lymphoblastic leukemia or 2) a method of using said fish as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is maintained for reasons of record set forth at pages 3-8 of the office action dated 11/22/2006.

The claims are broadly drawn to a transgenic fish comprising a transgene encoding any oncogene operably linked to any promoter. Dependent claims limit the genera of promoters and oncogenes, for example to T-cell specific promoter. Claims 24 and 35 are drawn specifically to a transgenic fish whose genome comprises a cMYC gene operably linked to a RAG2 promoter; however, the claims fail to require that the cMYC gene be expressed. Claims 1,24 and 35 now require that the fish exihibit an oncogenic phenotype, which is an overly broad genus of phenotypes. Claims 36,37,39-59 and 67-74 are drawn to screening methods using the claimed fish. In addition to the breadth set forth for the fish, above, the method claims broadly encompass any methodology of determining if a drug or agent modulates oncogene mediated neoplastic transformation and does not require any type of comparison to the an untreated control fish.

The specification has taught generating transient transfected and germline transgenic zebrafish expressing a mcMYC transgene operably linked to the zebrafish Rag2 promoter, in T-cells. mcMYC, EGFP-mcMYC, and MYC-ER (page 41, paragraph 2), constructs were used in independent experiments. All constructs led to leukemic phenotypes in the fish, including the MYC-ER construct in the absence of tamoxifen, albeit at a lower frequency. The specification has not taught the genus of transgenic fish encompassed by the claims or methods of using them. Examples 3-5 provide prophetic teachings of developing other transgenic fish models of cancers. However, the specification does not provide the guidance necessary to make any transgenic fish expressing any oncogene other than cMYC under the

control of the RAG2 promoter, in detail sufficient enough to overcome the unpredictability that is well-established in the art of making transgenic animals.

The unpredictability in the art is set forth at page 5, last paragraph-page 7 of the office action dated 11/22/2006. In general, the unpredictabilities relevant to the instantly claimed invention are with respect to the phenotype that is caused by expression of a transgene, the activity of promoters and the levels of expression and spatial/temporal expression control the will cause. With this in mind, and given the guidance in the specification, it would not have been predictable at the time of filing, given the guidance in the specification, what phenotypic effect any of the claimed transgenes would have other than the expression of cMYC under the control of the RAG2 promoter as taught by the specification. Given the lack of predictability of various promoters in transgenic fish, it is also not predictable that any given transgene will be expressed. Thus, for a fish of the instant invention to have a use, it must express the transgene. Such expression is not required by the claims (see pages 7-8 of the office action dated 11/22/2006).

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that the claims, as amended are drawn to transgenic fish whose genome has stably integrated therein an oncogene operably linked to a promoter wherein the oncogene induces an oncogenic phenotype. Applicant's argue that at least two working examples of the claimed transgenic fish are disclosed (page 10 of Applicant's Remarks). Applicant points to Example 1, disclosing a transgenic fish expressing a cMYC oncogene operably linked to a Rag2 promoter wherin the oncogene induced a T-cell acute lymphoblastic leukemia. Example 2 discloses a transgenic fish expressing BCL-2 operably linked to a Rag2 promoter wherein an anti-apoptotic phenotype results. Applicant discloses that Examples 3-5 are prophetic. Applicant asserts that the person of ordinary skill in the art would recognize that heterologous promoters in fish could express and oncogene in levels sufficient to result in an oncogenic

phenotype. The conservation of genetic pathways controlling signal transduction are highly conserved in zebrafish and that these properties have established the zebrafish as a model system for studies of vertebrate development, incluyding cnacers.

In response, Applicant has provided two examples of a promoter/oncogene combination that leads to a phenotype that is associated with cancers. Neither lead to "any" oncogenic phenotype as now claimed. This is not sufficient to demonstrate that any, or even a significant number, of oncogenes will cause such phenotypes when operably linked to any, or even a significant number, of heterologous promoters. The art has established a significant unpredictability of transgene effect related to conservation of gene function and regulation of heterologous gene promoters, as well as other effects of general nature to transgenesis. The claims are very broad with respect to the identity of the transgene and the phenotypic effect observed. The specification fails to provide enough guidance such that one of skill would know which oncogene and which promoter will result in any given or desired phenotype. One of skill in the art would not only need to make the fish and determine if a phenotype of oncogenic nature is caused, but also what that effect is such that one of skill in the art would know how to use the fish.

Applicant refers to postfiling art that demonstrates that it would not require undue experimentation to develop transgenic fish models comprising oncogenes operably linked to promoters wherein an oncogenic phenotype is expressed. Applicant argues that in light of these post-filing findings, it would not have required undue experimentation to have done such at the time of filing.

In response, the experimentation and findings reported post-filing are examples of the experimentation necessary to overcome the art recognized unpredictabilities. Each promoter/oncogene combination resulted in a different oncogenic phenotype (rhabdomyosarcoma, melanoma, etc). Additionally, some combinations that may not have had a phenotypic effect would not be reported. Post-filing findings in the art fail to overcome the unpredictabilities known and established at the time of filing.

It is noted, that the claims are not enabled for the breadth of "oncogenic phenotype" as claimed. This is a broad genus of phenotypes not supported by the specification (see below). The specification teaches the the Rag2-mcMYC transgene leads to T-cell lymphoblastic leukemia and does not teach other phenotypes. It is not know, a priori, what phenotypes, including what oncogenic phenotypes, other transgenes would cause in a fish.

Applicant argues with respect to the method claims that use for a drug that increases oncogenic mediated neoplastic or hyperplastic transformation would be readily apparent to one skilled in the art because a patient with a mutation that suppresses oncogene mediated neoplastic or hyperplastic transformation could be treated with a drug that increases such oncogene-mediated neoplastic or hyperplastic transformation to test whether the drug reverses the anti-oncogenic effects of the mutation Page 12, paragraph 3).

In response, the claimed method is to screening for agents that "modulate" oncogene-mediated neoplastic or hyperplastic transformation using a transgenic fish. The issue at hand is the breadth of the term "modulate" in the claim. A fish with a cancerous phenotype can be used to screen for agents that treat or diminish the cancerous phenotype. The specification does not enable use of the claimed fish to screen for upregulators of cancer. Of prime importance is how one would carry out such a method. If a fish already exhibits a cancerous phenotype, it is not known how to test an agent for cancer causing effects using said fish.

With respect to the claims not requiring a control or comparison to a baseline, Applicant argues that a determination is made as to whether the test drug modulates the oncogenic phenotype in the fish

and that a second untreated fish is not necessary. One can observe the treated fish before and after treatement.

In response, while it is agreed that a second, control fish is not necessary, the claims should recite a comparison step of before and after treatment or otherwise recite what is an indicator of the desired agent (see beginning of rejection, above). For example, a step of classifying a test drug as a modulator of a phenotype if the phenotype is altered by the treatment should be added in appropriate terms.

Written Description

Claims 18 and 53 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for reasons of record set forth at pages 9-10 of the office action dated 11/22/2006.

The specification has described the MYC gene and the art has established functional conservation of MYC homologues in sufficient detail. The specification, however, has not described an oncogene substantially similar to cMYC in terms of its structural or functional identity. In fact, the specification has not set forth any definition of what is intended by the terminology "substantially similar to".

Applicant's arguments have been fully considered and are not persuasive.

Applicant argues that the specification defines "substantially similar" as sufficiently similar to a reference nucleotide that a nucleotide sequence will hybridize to under moderately stringent conditions. The specification further requires that a "substantially similar" oncogene encode a protein having cell neoplastic transformation ability.

In response, while it is agreed that the specification may define what is intended, the specification has not described the genus in relevant identifying characteristics. Hybridization of nucleic acids fails to provide a relevant and necessary activity for the claimed invention. Additionally, the specification has not established which known oncogenes would have activity that would be considered "similar" to cMyc. For instance, it is not known if the gene would need to have similar phenotypic effects when introduced as a transgene, whether it would need to act in the same pathway, or whether it need to play a similar cellular role.

New Matter

The following rejections are necessitated by amendment.

Claims 1,2,4-24 and 26-35 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims have been amended such that they now contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The original disclosure fails to recite the limitation of an oncogenic phenotype. Applicants point to Examples 1 and 2 for support for this limitation but support for such breadth is not found. Further, a key word search of the specification fails to find disclosure of this limitation anywhere in the specification as initially filed. Therefore, since the specification as filed does not contain support for the term "oncogenic phenotype", it is considered to be new matter. See M.P.E.P. 608.04(a). Applicant is required to cancel the new matter.

Claims 36-37,39-59 and 67-74 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims have been amended such that they now contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. The original disclosure fails to recite the limitation of any oncogene mediated neoplastic or hyperplastic transformation. Applicants point to Examples 1 and 2 for support for this limitation but support for such breadth is not found. Further, a key word search of the specification fails to find disclosure of this limitation anywhere in the specification as initially filed. Therefore, since the specification as filed does not contain support for the term "oncogene-mediated neoplastic or hyperplastic transformation", it is considered to be new matter. See M.P.E.P. 608.04(a). Applicant is required to cancel the new matter.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 53 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 53 are vague and indefinite because the limitation "substantially similar" is conditional and no single set of defining conditions has been recited in the claim or the instant specification. The claim is not just broad by the use of the term but is indefinite because it is not known what is intended to be encompassed by the claim because no definition of "substantially similar" is set forth and the metes and bounds cannot be determined.

Applicant argues that the metes and bounds of the terminology is clear as argued under Written Description. Likewise, these arguments are addressed above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio
Primary Examiner
Art Unit 1632